A response by Servier to the clarification document

Servier is pleased to provide the requested information in response to the questions posed by the DSU.

1*).* ***"We request that original documentation detailing Servier's communications with the EMA be provided."***

Servier is pleased to enclose the original documentation, as requested, concerning the communication between Servier and the EMA (ref: Appendix 1).

2). ***"Please would you provide copies of the documentation in which, you assert, a precedent is set for the regulatory approval of strontium ranelate on the basis of a post-hoc subgroup?"***

Servier argues that there was a precedent for the regulatory approval of osteoporosis therapies, based on subgroup analyses, prior to the licensing of Strontium ranelate. For example, risedronate and alendronate were granted marketing authorisations for the prevention of osteoporotic hip fractures based on post hoc and subgroup analyses respectively. (McClung 2001 and the FIT 1 & FIT 2 studies). Such a precedent was referred to in the Protelos European Public Assessment Report (ref: Protelos EPAR, scientific discussion 2005, p.18):

"To this end, the applicant presented post hoc subset analyses at three years for a revised target population aged ≥74 years and with femoral neck BMD T-score ≤-3 SD (≤-2.4 SD NHANES III), for which efficacy of the same order of magnitude as shown for bisphosphonates is indicated. This has now been further supported by consistent risk reduction estimates from four-year follow-up and from the whole TROPOS population meeting the specified BMD criteria. This type of approach has regulatory precedent and is considered acceptable to support a therapeutic indication."

A similar statement is also appears on p.22 in the scientific discussion of the Protelos EPAR 2005:

"For this indication, the demonstrated effect of Sr ranelate 2 g/d appears comparable with that of bisphosphonates, and the strategy to accept a therapeutic indication partly based on post hoc analysis of a revised target population of particular medical interest has regulatory precedent in the European licensing of bisphosphonates."

"We note that the table caption refers to "French SPC"; do you wish to draw our attention to decision-making in that jurisdiction? Please provide copies of all documentation that you consider relevant to this question"

Servier wishes to draw the attention of the DSU to sections of the French SPC for risedronate (ref: Appendix 2a: p. 6, section Pharmacodynamie) and alendronate (ref: Appendix 2b: p. 7, section Pharmacodynamie)

3***). "Please provide clarification regarding the number of people in the placebo arms of TROPOS and SOTI analysed for underlying risk of hip fracture. In Table 1 on p. 12 of Appendix A, the total number of participants analysed (for prevalence of hip fracture relative to T-score) sums to 3246 whereas, in Table 2 on p. 13, the total number of participants analysed (for prevalence of hip fracture relative to age) sums to 3256. This latter number also apparently corresponds to the population analysed according to prevalent fragility fracture (text on p. 12)."***

There are 10 patients with BMD femoral T-scores missing at baseline for the three year analysis and hence they are not included in the placebo analysis referred to in Table 1 p.12. However this was not the case with age and these patients could be included and they are therefore seen in Table 2 p.13. Please see the table below:

IAE FAS periph Placebo group (N=3256)		BMD femoral T-score	
		Not missing	**Missing**
Age	Not missing	3246	**10**
	Missing	0	0

"These numbers are inconsistent and, moreover, do not correspond directly to the population sizes of the professed data-source: as far as we are aware, the numbers randomised in TROPOS + SOTI were (2537+821=) 3358, and the FAS ("ITT") populations sum to (2453+723=) 3176. Are you able to account for the apparent discrepancies?"

The FAS for TROPOS + SOTI (ITT) was strictly defined, as in TROPOS, to examine any event of a peripheral nature. The placebo group corresponds to **803** for SOTI and 2453 for TROPOS, a total of 3256 patients

4***). "Please provide more detailed information regarding the methods according to which the pooled placebo arm was "screened" for risk factors for hip fracture. In particular, For age, how was the particular threshold of 74 arrived at and what other values were investigated?"***

The selection criteria for the analysed subgroup were both biologically and statistically justified. The particular threshold of 74 was arrived at because:

- Age is a known risk factor for osteoporosis, and the risk of fracture increases exponentially after the age of 74 years (*Donaldson et al*.)
- It is consistent with the inclusion criteria of the study, and is in line with established evidence on fracture risk.
- In the placebo arm of TROPOS, women aged ≥74 years had a significantly higher risk of hip fracture than younger women.

"Please provide full incidence data for hip fracture by age in the pooled placebo population (i.e. numbers of participants experiencing events at each year of age)."

The number of patients at risk and the number of proximal femur fractures over 3 years in the placebo group by age is provide in the table below:

Age	N Patients at risk	N Events
50	1	0
51	2	0
52	2	0
53	4	0
54	6	0
55	9	0
56	10	1
57	10	0
58	13	0

59	10	0
60	25	0
61	16	0
62	22	1
63	31	0
64	32	1
65	34	0
66	45	1
67	33	0
68	43	0
69	56	0
70	225	2
71	227	2
72	223	2
73	223	2
74	238	6
75	245	6
76	250	4
77	199	6
78	167	3
79	106	4
80	113	3
81	113	2
82	104	8
83	102	1
84	91	9
85	58	3
86	45	3
87	45	4
88	32	1
89	14	1
90	15	1
91	6	1
92	6	0
93	3	1
94	1	0
95		
96	1	0
97		
98		
99		
100		

The paucity of events overall in the above table warranted a further investigation of the placebo data to ensure accurate calculation of fracture incidences and ease of interpretation. Therefore the SOTI and TROPOS populations were analysed, and repeatedly checked, in two sub-populations according to the age of the patient. In the

following table the boundary runs from 70 to 85 years. Between 70 and 80 years old, the most discriminating cut off is 74 years with a RR = 4.27 and hence this was the threshold chosen.

	N Patients at risk		N Events		Incidence E, SE, 95% CI						Relative risk
Cutoff	<cutoff	>=cutoff	<cutoff	>=cutoff	<cutoff			>=cutoff			
70	404	2852	4	75	1.05%	0.52%	[0.03% ; 2.08%]	3.39%	0.39%	[2.62% ; 4.15%]	3.23
71	629	2627	6	73	1.04%	0.42%	[0.21% ; 1.87%]	3.61%	0.42%	[2.79% ; 4.43%]	3.47
72	856	2400	8	71	1.05%	0.37%	[0.32% ; 1.78%]	3.87%	0.46%	[2.98% ; 4.77%]	3.69
73	1079	2177	10	69	1.06%	0.33%	[0.40% ; 1.71%]	4.18%	0.50%	[3.20% ; 5.16%]	3.94
74	1302	1954	12	67	1.07%	0.31%	[0.47% ; 1.67%]	4.57%	0.55%	[3.48% ; 5.66%]	4.27
75	1540	1716	18	61	1.40%	0.33%	[0.75% ; 2.04%]	4.75%	0.60%	[3.56% ; 5.93%]	3.39
76	1785	1471	24	55	1.61%	0.33%	[0.97% ; 2.26%]	5.06%	0.68%	[3.73% ; 6.39%]	3.14
77	2035	1221	28	51	1.64%	0.31%	[1.04% ; 2.25%]	5.83%	0.81%	[4.24% ; 7.42%]	3.55
78	2234	1022	34	45	1.83%	0.31%	[1.22% ; 2.44%]	6.23%	0.92%	[4.42% ; 8.03%]	3.40
79	2401	855	37	42	1.85%	0.30%	[1.25% ; 2.44%]	7.17%	1.10%	[5.02% ; 9.32%]	3.88
80	2507	749	41	38	1.99%	0.31%	[1.38% ; 2.60%]	7.35%	1.18%	[5.03% ; 9.67%]	3.69
81	2620	636	44	35	2.05%	0.31%	[1.44% ; 2.65%]	8.19%	1.38%	[5.49% ; 10.89%]	4.00
82	2733	523	46	33	2.05%	0.30%	[1.46% ; 2.64%]	9.84%	1.70%	[6.52% ; 13.17%]	4.80
83	2837	419	54	25	2.34%	0.32%	[1.72% ; 2.96%]	9.37%	1.87%	[5.70% ; 13.04%]	4.00
84	2939	317	55	24	2.31%	0.31%	[1.70% ; 2.91%]	12.28%	2.48%	[7.42% ; 17.14%]	5.32
85	3030	226	64	15	2.64%	0.33%	[2.00% ; 3.29%]	9.80%	2.55%	[4.80% ; 14.81%]	3.71

"Were any other baseline variables considered?"

Apart from age, T-score and previous fracture history no other baseline variables were analysed. This approach was appropriate as, at the time of submission, these three variables were acknowledged as major risk factors for osteoporotic fracture.

5). ***"We note your comment at the foot of Table 3 (p. 33, Appendix A) that the 4-year dataset includes two participants who were not included in the 3-year analysis. Have you undertaken an updated analysis of relative risk at 3 years with these additional individuals included? If so, please provide the results."***

The following analysis of cumulative incidence of new hip fracture at 3 years including the two participants who were not initially included in the 3-year analysis (but who were included in the 5-year analysis), for the subgroup at increased risk (Age $\geq$ 74 years and femoral T score $\leq$ -3) is summarised in the table below. Please note these results are comparable to those which do not include the two patients mentioned in this question.

	Pts. with femoral neck BMD T-score ≤-3.0 & age ≥74 years	
	Strontium ranelate	Placebo
Total number of patients at risk	982	997
Total number of events	30	46
Cumulative incidence over 3 years: RR (SE); 95% CI	**RR=0.64 (0.14); 95% CI [0.413; 0.99] P = 0.047**	

6). ***"Please provide basic data (numbers at risk & numbers of hip fractures per randomized group – SR vs placebo) and the estimate of the relative risk of hip fracture, and 95% Confidence interval, for the remainder of the TROPOS population that are not included in the subgroup i.e. point 15 of the original request from NICE. "***

Servier respectfully acknowledges the request for further data. However, as stated in the answer to point 15 of the original document, due to the small populations and low frequency of fractures in the requested subgroups, such information would be unable to provide reliable or robust estimates for the efficacy of strontium ranelate.

7***). "Please provide basic data (as defined in 6), estimate and 95% CI from the SOTI trial data for the relative risk of hip fracture for the same subgroup of patients as from the TROPOS trial (i.e. women aged ≥74 years with a BMD T-score equivalent to ≤−2.4 according to NHANES III normative data) as well as for those not in the subgroup."***

Servier respectfully acknowledges the request for further exploratory analyses from the SOTI trial. However, SOTI was powered and intended to analyse vertebral fractures and not hip fracture. The incidence of hip fracture was low in this study with a total of 9 occurring over 3 years in the group of patients at increased risk of fracture (women aged ≥74 years with a BMD T-score equivalent to ≤−2.4 according to NHANES III normative data.) Therefore any interpretation from SOTI based on this data would be unable to provide reliable or robust estimates for the efficacy of strontium ranelate on hip fractures.

8***). "Please provide the following information (relative risk of hip fracture and CI, number of events and numbers at risk) for each of the following 6 patient subgroups:***

a. ***Age >=74yrs***

	Patients with age ≥ 74	
	Strontium ranelate	**Placebo**
FAS		
Total number of patients	1711	1719
Total number of patients with at least one incident hip fracture	46	65
RR (SE); 95% CI	**RR=0.73 (0.14); 95% CI [0.498; 1.059]**	

b. ***Femoral BMD T-score <=-3.0***

	Patients with a femoral neck BMD T-score ≤-3.0	
	Strontium ranelate	Placebo
FAS		
Total number of patients	1374	1373
Total number of patients with at least one incident hip fracture	43	59
RR (SE); 95% CI	**RR=0.70 (0.14); 95% CI [0.473; 1.041]**	

c. Prior fragility fracture only

d. Femoral BMD T-score <=-3.0 and prior fragility fracture

e. Age >=74yrs and prior fragility fracture

f. Age >=74yrs and femoral BMD T-score <=-3.0 and prior fragility fracture

Servier respectfully acknowledges the request for information concerning the incidence of hip fracture and its association with prior fragility fracture. However, as previously described, the TROPOS study population showed no clear difference in hip fracture incidence between patients with or without prior fracture. Hip fracture incidence was 2.7% in those patients with a prevalent fragility fracture (n=2053), and 3.4% in those patients with no prior fragility fracture (n=1203). Furthermore the numbers of patients in the latter patient subgroups suggested are very small. Hence such analyses are highly unlikely to yield reliable or robust estimates for the efficacy of Strontium ranelate.

9). ***"Please provide the individual patient level data from the TROPOS trial in order for the DSU to replicate your analyses."***

Servier acknowledges the request for individual patient data. We wish to reassure the DSU that all statistical analyses carried out on the TROPOS data are appropriate, valid and correct. Such analyses have been reviewed and accepted by the EMA during registration, certified and verified by Servier's statistics department. We feel that supplying such individual patient level data is therefore unnecessary. We also

feel providing such data would be beyond the usual requirements placed upon manufacturers by NICE in their appraisal of treatments.

10). ***"If you want to reconsider the confidentiality marking of your submission, please let us know. "***

The original Servier submission with Appendices A & B have been revised with regards to the commercial in confidence status. These will be sent as a separate document.